AMENDMENT

I. In the Specification

Please amend the specification as follows:

Please replace the paragraph on page 2, line 32 to page 3, line 10, with the following paragraph:

> The detection of nucleic acids solely by probe hybridization has only a limited sensitivity. Thus only a sensitivity in the ~~pg~~ picogram to ~~fg~~ femtogram range is possible even when using sensitive detection marker groups such as ^{32}P, digoxigenin, biotin, fluorescein, ruthenium, chelates, fluorescein, rhodamine or AMCA. However, sensitivities in the ~~ag~~ attogram range and a high test specificity is required for a sensitive nucleic acid test especially in the medical-diagnostic field. This applies to the detection of exogenous nucleic acids e.g. in the form of infectious pathogens as well as the detection of the presence or absence or change of endogenous nucleic acids. A high test sensitivity and test specificity is, however, also very important in the other stated fields of application.

Please replace the paragraph on page 13, line 19 to page 14, line 1 with the following paragraph:

> The invention concerns a method for the production of a plurality of amplificates of a section ~~of this~~ of a nucleic acid with the aid of two primers, one of which can bind to a first binding sequence ~~(A)~~ (A'), which is complementary to a sequence (A) of a strand of the nucleic ~~acid~~ acid, and the other can bind to a second binding sequence ~~(C')~~ (C) ~~which is complementary to a sequence C~~ which is located in the 3' direction from A and does not overlap A, contacting the amplificates with a probe having a binding sequence D which can bind either to a third sequence (B) located between the sequences A and C or to the complement (B') thereof, and detecting the formation of a hybrid of an amplificate and the probe wherein the third sequence (B) located between the binding sequences A and C or the complement (B') thereof contains no nucleotides that are not part of the sequence section E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto.

Please replace the paragraph on page 15, lines 15-16 with the following paragraphs:

Fig. 8 ~~to 10 show~~ shows preferred sequences for primers and probes for the HCV test.

Fig. 9 shows preferred sequences for primers and probes for the HCV test.

Fig. 10 shows preferred sequences for primers and probes for the HCV test.

Please replace the paragraph on page 19, line 30 to page 21, line 23 with the following paragraph:

In the first essential step of the method according to the invention a segment of the nucleic acid to be detected is amplified. This segment is also referred to as an amplicon in the following. It is essential that this contains the sequence region between the outer ends of the binding sequences ~~A and C'~~ A' and C or of the complement thereof ~~of the primers~~ (the primer binding regions) and contains the binding region E of the probe or of the complement thereof. According to the present invention the amplicon (preferably the total length of the sequences of the regions A, B and C) is preferably shorter than 100 nucleotides, particularly preferably shorter than 60 nucleotides, but preferably longer than 40 nucleotides. However, this does not mean that the total length of the amplificates cannot be larger e.g. when the primers have additional nucleotides. Amplification methods are used which allow an amplification of the nucleic acid to be detected or the complement thereof and result in the formation of tripartite mini-nucleic acid amplification products [mini chain reaction (MCR)]. In principle all nucleic acid amplification methods that are known in the prior art can be used for this. Target-specific nucleic acid amplification reactions are preferably used. Theoretically exponential target-specific nucleic acid amplification reactions are particularly preferably used in which an anti-parallel replication of the nucleic acid to be detected or of its complement is carried out e.g. elongation-based reactions such as the polymerase chain reaction (PCR for deoxyribonucleic acids, RT-PCR for ribonucleic acids) or transcription-based reactions such as e .g. nucleic acid sequence based amplification (NASBA)

or transcription mediated amplification (TMA). Thermocyclic exponential elongation-based nucleic acid amplification reactions are particularly preferred such as e.g. the polymerase chain reaction. The nucleic acids to be detected or complements thereof which are used for the amplification can be present in the form of single-stranded or double-stranded deoxyribonucleic acids or ribonucleic acids. The aim of the amplification reaction (amplification) is to produce numerous amplificates of a segment of the nucleic acid to be detected. Hence an amplificate is understood as any molecular species produced by using sequence information of the nucleic acid. In particular the term refers to nucleic acids. The term "amplificate" includes single-stranded as well as double-stranded nucleic acids. In addition to the regions containing the sequence information of the underlying nucleic acid (amplicon), an amplificate can also contain additional regions which are not directly related to sequences of the nucleic acid to be amplified that are outside the ends of the primer binding sites which face away from another. Such sequences with a length of more than 15 nucleotides preferably do not occur on the nucleic acid to be detected or its complement and cannot hybridize with it by direct base pairing. Hence amplificates can either hybridize with the nucleic acid to be detected itself or with its complement. Amplificates are for example also products of an asymmetric amplification i.e. an amplification in which the two strands are formed in different amounts (e.g. by using different amounts of primers) or in which one of the two strands is subsequently destroyed (e.g. by RNAse).

Please replace the paragraph on page 25, line 25 to page 26, line 1 with the following paragraph:

In the present invention the segment of the nucleic acid from which it is intended to produce a plurality of amplificates is selected such that it contains three regions A, B and C. Regions A and C are regions selected such that one primer can use the complement of sequence A as the binding sequence and ~~the complement of~~ the region C can serve as the binding sequence for the other primer. A complement within the sense of the present invention is understood as a nucleic acid or nucleic acid sequence which is

essentially complementary to a certain other nucleic acid e.g. a sequence region e.g. of an amplificate or of the nucleic acid to be detected.

Please replace the paragraph on page 42, line 34 to page 43, line 5 with the following paragraph:

Homologies to other genomes (sequences) can be identified with the aid of a defined initial sequence. A search engine with the name "BLAST" (basis local alignment search tool) that is accessible to anyone via the internet ~~(homepage address:>http://www.ncbi.nlm.nih.gov/BLAST/<)~~ can for example be used.

Please replace the paragraph on page 47, lines 25 to 28 with the following paragraph:

The primers preferably bind to the binding sequences ~~A or C'~~ A' or C as described above and the probe preferably binds either to a region B located between the ends of the binding sequences ~~A and C'~~ A' and C or to the complement thereof.

Please replace the abstract paragraph on page 76, lines 3 to 17 with the following paragraph:

Method for the detection of a nucleic acid comprising the production of a plurality of amplificates of a section of this nucleic acid with the aid of two primers, one of which can bind to a binding ~~sequence A~~ sequence A', which is complementary to a sequence A of the nucleic ~~acid~~ acid, and the other can bind to a binding ~~sequence C' which is complementary to a~~ sequence C which is located in the 3' direction from A and does not overlap with A, contacting the amplificates with a probe having a binding sequence D which can bind either to a sequence B which is located between the sequences A and C or to the complement thereof, and detecting the formation of a hybrid of the amplificate and probe where the sequence located between the binding sequences A' and C contains no nucleotides that do not belong to the binding sequence D of the probe or its complement D'.

II. In the Claims

Please cancel Claims 16-25 and amend the claims to read as follows:

1. (Currently Amended) A method for the detection of a nucleic acid comprising the steps:

(a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which ~~can bind~~ binds to a binding ~~sequence A~~ sequence A', which is complementary to a sequence A of one strand of the nucleic acid, and the other ~~can bind~~ binds to a binding sequence ~~C' which is essentially complementary to a sequence~~ C which is located in the 3' direction from A and does not overlap A,

(b)- contacting the amplificates with a probe having a binding sequence D which ~~can bind~~ binds either to a ~~sequence B,~~ sequence B or to the complement thereof, wherein the sequence B is located between the sequences A and C ~~or to the complement thereof~~, and

(c)- detecting the formation of a hybrid of the amplificate and probe,

wherein the sequence located between the ~~binding~~ sequences A and C contains no nucleotides or less than 3 nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto and the amplificates are shorter than 100 nucleotides.

2. (Previously Amended) The method of claim 1, wherein the binding sequence D of the probe overlaps one or both binding sequences of the primers.

3. (Currently Amended) The method of claim 1, wherein at least one of the primers has nucleotides in its non-extendible part which do not hybridize ~~directly~~ with the nucleic acid to be detected or with its complement.

4. (Currently Amended) The method of claim 1, wherein at least one of the ~~binding sequences~~ primers or probe is not specific for the nucleic acid to be detected.

5. (Previously Amended) The method of claim 1, wherein the total length of the amplificate does not exceed 74 nucleotides.

6. (Currently Amended) The method of claim 1, wherein at least one of the primers is ~~immobilizably-labelled~~ immobilizably-labeled and the probe is ~~detectably-labelled~~ detectably-labeled.

7. (Currently Amended) The method of claim 1, wherein at least one of the primers is ~~detectably-labelled~~ detectably-labeled and the probe is ~~immobilizably-labelled~~ immobilizably-labeled or is immobilized.

8. (Currently Amended) The method of claim 1, wherein the probe is ~~labelled~~ labeled with a fluorescence quencher as well as with a fluorescent dye.

9. (Currently Amended) The method of claim 1, wherein one of the primers is ~~labelled~~ labeled with a first energy transfer component and the probe is ~~labelled~~ labeled with a second energy transfer component which is different from the first energy transfer component.

10. (Previously Amended) The method of claim 1, wherein the amplificate is detected by physical and/or spectroscopic methods.

11. (Previously Amended) The method of claim 1, wherein at least one of the primers is not specific for the nucleic acid to be detected.

12. (Previously Amended) The method of claim 11, wherein two of the primers are not specific for the nucleic acid to be detected.

13. (Previously Amended) The method of claim 11, wherein the probe is not specific for the nucleic acid to be detected.

14. (Previously Amended) The method of claim 1, wherein nucleotides which are each complementary to A, G, C and T are used in the amplification.

15. (Previously Amended) The method of claim 1, wherein the amplificates are detected by means of mass spectroscopy.

16-25. (Cancelled)

REMARKS

Claims 1-15 are pending and under consideration in the instant application. With this amendment, the specification and Claims 1, 3, 4, and 6-9 are amended. Following entry of the present amendment, Claims 1-15 are pending and under consideration.

I. The Amendments to the Specification

The present application describes, in part, a method for detecting a nucleic acid by amplifying the nucleic acid and detecting the amplificate. In certain portions, the specification mistakenly describes methods for amplifying the nucleic acid to be detected that identify the wrong strand of the nucleic acid to be amplified as the primer binding region. Specifically, the specification in places describes the primer binding regions to be A and C' rather than A' and C, as described by other portions of the specification and the figures. Accordingly, Applicants are amending the portions of the specification that mistakenly describe the primer binding regions to be A and C' to conform to the portions of the application that correctly describe the primer binding regions as A' and C.

In particular, the amendments to the specification on page 13, line 19 to page 14, line 1; page 19, line 30 to page 21, line 23; page 25, line 25 to page 26, line 1; and page 47, lines 25 to 28, and to the abstract on page 76, lines 3 to 17, conform the mistaken description presented by these portions of the specification to the correct portions of the application. The specification, for example, at page 54, lines 1 to 12; page 60, line 12 to page 62, line 11; the table on page 63; and the table on page 65, and Figures 2, 9, and 10 each correctly describe the primer binding regions as A' and C and support the amendments to the specification discussed above.

For example, Figure 2 depicts an amplificate comprising sequences A, B and C, wherein C is located in the 3' direction of A. Also depicted is the complement of the amplificate comprising sequences A', B' and C'. One of ordinary skill in the art will readily recognize from this depiction that the primers must bind to sequences A' and C rather than A and C' to produce such an amplificate. The Examples provided in the specification, and Figures 9 and 10 also demonstrate the correct directionality and binding of primers that bind sequences corresponding to sequences A and C'. For instance, the table on page 63 provides examples of primers that were used to amplify regions of the HIV genome. In each case, the forward primer (for example, SK 462) is essentially identical to the sequence at the 5' region of the amplificate, while the reverse primer (for example, SK 431) is complementary to the

sequence at the 3' region of the amplificate. Similarly, the table on page 65 provides examples of primers that were used to amplify regions of the HBV genome. In each example of pairs of primers used, the forward primer corresponds to the sequence at the 5' region of the amplificate, while the reverse primer is complementary to the sequence at the 3' region of the amplificate. Thus, for each Example, the forward primer binds a sequence complementary to the strand corresponding to the primer, which sequence corresponds to a sequence A' which is essentially complementary to the sequence A. Similarly, the reverse primer of each example binds to a sequence C, which is 3' of A on the same strand.

In addition, Figures 9 and 10 provide a section of the HCV genome from positions 261 to 333 in the 5' to 3' direction. The forward primer (for example, CK10) is essentially identical to the sequence at the 5' region and the reverse primer (CK20) is complementary to the sequence at the 3' region. The forward primer, CK10, binds to the complementary strand of the HCV strand provided, corresponding to binding sequence A'. The reverse primer, CK20, binds to binding sequence C, which is in the 3' direction from A. Thus, certain parts of the present application properly describe the primer binding regions used to produce the amplificates to be A' and C, rather than A and C'. Accordingly, the amendments to the specification and to the abstract to conform the mistaken portions of the specification to the correct description are fully supported by the application as filed.

The specification has also been amended on page 2, line 32 to page 3, line 10; page 15, lines 15-16; and on page 42, line 34 to page 43, line 5 in response to the PTO's objections to the specification. The amendment on page 2, line 32 to page 3, line 10 replaces the abbreviations "pg," "fg," and "ag" with the full terms "picogram," "femtogram," and "attogram." Applicants respectfully submit that in the context of this paragraph, *i.e.*, discussion of the sensitivity of nucleic acid detection methods, one of ordinary skill in the art would recognize that these abbreviations refer to the amount of nucleic acids that can be detected with these methods. Thus, the amendment on page 2, line 32 to page 3, line 10 is fully supported by the specification.

Further, the amendment to page 15, lines 15-16 replaces the combined description of Figures 8-10 with individual descriptions of Figure 8, Figure 9, and Figure 10. The amendment to the specification at page 15, lines 15-16 is fully supported by the specification at, for example, page 15, lines 15-16.

Finally, the amendment of the specification at page 42, line 34 to page 43, line 5 merely deletes an embedded hyperlink. Accordingly, this amendment does not change the disclosure of the application and as such is fully supported by the specification as filed.

Given the support in the specification, including the examples and figures, the amendments to the specification do not introduce new matter. Accordingly, entry of the amendments to the specification under 37 C.F.R § 1.111 is hereby respectfully requested.

II. The Amendments to the Claims

In the present amendment, Claims 1, 3, 4, and 6-9 are amended, while Claims 16-25 are cancelled. Thus, following entry of the present amendment, Claims 1-15 are pending and under consideration.

Like the erroneous portions of the specification discussed above, Claim 1 mistakenly described the primer binding regions to be A and C', rather than the correct primer binding regions A' and C. In addition, the PTO has rejected Claim 1 as indefinite over the recitation of "a probe having a binding sequence D which can bind to a sequence B located between the sequences A and C, or to the complement thereof." Therefore, Claim 1 has been amended to recite a method for the detection of a nucleic acid comprising the steps (a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which can bind to a binding sequence A', which is essentially complementary to a sequence A of one strand of the nucleic acid, and the other can bind to a binding sequence C which is located in the 3' direction from A and does not overlap A, (b)- contacting the amplificates with a probe having a binding sequence D which can bind either to a sequence B or to the complement thereof, wherein the sequence B is located between the sequences A and C, and (c)- detecting the formation of a hybrid of the amplificate and probe, wherein the sequence located between the binding sequences A and C contains no nucleotides or less than three nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto.

The amendments to Claim 1 are supported, in part, by the same portions of the specification that support the amendments to the specification that correct the description of the primer binding regions, as described above. For example, support for amended Claim 1 can be found in the specification at page 54, lines 1 to 12; page 60, line 12 to page 62, line 11; the table on page 63; and the table on page 65; in Figures 2, 9, and 10; and in Claim 1 as originally filed. Figure 2 depicts the amplificate and complement of the amplificate that is produced by primers that bind to sequences A' and C. In addition, the specification at page 54, lines 1 to 12 and page 60, line 12 to page 62, line 11 and Figures 9 and 10 further support amended Claim 1 by describing the HCV genomic sequence and amplicon formed therefrom, along with primers for use in the examples. The table on page 63 and the table on page 65

additionally support the amendment to Claim 1 by providing examples of forward and reverse primers that can be used to amplify regions of the HIV and HBV genomes, respectively. Finally, Claim 1 as filed recites that the probe comprises a binding sequence D binds to a sequence B which is between sequences A and C or to the complement thereof. Therefore, Applicants respectfully submit that the amendments to Claim 1 are fully supported by the application as filed.

Further, Claim 3 has been amended to recite that at least one of the primers has nucleotides in its non-extendible part which do not hybridize with the nucleic acid to be detected, or with its complement, thereby deleting the requirement that the primer "not directly hybridize" with the detectable nucleic acid. The amendment to Claim 3 is supported, for example, by Claim 3 as originally filed and by the specification at page 44, lines 25-29. Accordingly, Applicants respectfully submit that the amendment to Claim 3 is fully supported by the application as filed.

Claim 4 has been amended to recite that at least one of the primers or probes, rather than the binding sequences, are not specific for the nucleic acid to be detected. In addition, Claim 4 has been amended to clarify that the probe can bind to either binding sequence D or to the complement thereof. Support for the amendment to Claim 4 may be found, for example, in Claims 4, 11 and 13 as originally filed, and in the specification, for example, at page 42, lines 3-6, and at page 47, lines 25-28. Therefore, Applicants respectfully submit that the amendment to Claim 4 is fully supported by the specification and claims as filed.

Finally, Claims 6-9 have been amended to correctly spell the term "labeled." The amendments to Claims 6-9 are supported by, for example, Claims 6-9 as originally filed.

As shown by the foregoing, the amendments to the claims are fully supported by the specification, claims, and figures as originally filed. Therefore, Applicants respectfully submit that the amendments to Claims 1, 3, 4, and 6-9 do not introduce new matter. Accordingly, Applicants hereby respectfully request entry of the present amendment to the claims under 37 C.F.R. § 1.111.

III. The Objections to the Specification

The PTO objected to the specification on the basis of three informalities. Without acquiescing to the propriety of the objections, Applicants respectfully submit that the objections are moot in view of the amendments to the specification. Accordingly, Applicants respectfully request withdrawal of the objections to the specification.

IV. The Rejection of Claims 1-15 under 35 U.S.C. § 112, Second Paragraph

Claims 1-15 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. In particular, the PTO objects to elements of Claims 1, 3, 4, and 11-13, and rejects all the claims based upon their alleged indefiniteness or dependence on an allegedly indefinite claim. Without acquiescing to the propriety of this rejection, Applicants respectfully submit that the rejection of Claims 1-15 as indefinite is moot in view of the amendments to the claims, as shown below.

A. *The Legal Standard*

Under 35 U.S.C. § 112, second paragraph, a claim must particularly point out and distinctly claim the subject matter which the applicant regard as his invention. *See* 35 U.S.C. § 112, second paragraph. This statutory mandate is met when "one skilled in the art would understand the bounds of the claim when read in light of the specification." *See Personalized Media Communications, LLC v. International Trade Commission et al.*, 161 F.3d 696, 48 USPQ2d 1880 (Fed. Cir., 1998). "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *See id.*, quoting *Miles Lab., Inc. v. Shandon, Inc.* 997 F.2d 870, 238 USPQ2d 1123 (Fed. Cir., 1993).

B. *Claims 1, 3, 4, and 11-13 are not Indefinite as Amended*

Claim 1 stands rejected as allegedly indefinite over the recitation of "essentially complementary." Without acquiescing to the propriety of the rejection, Applicants have amended Claim 1 to recite that the binding sequence A' is complementary to a sequence A. Applicants respectfully submit that the ordinarily skilled artisan will understand the bounds of Claim 1 as amended based upon the art-recognized meaning of the term "complementary." The art-recognized meaning of the term "complementary" in reference to two single stranded nucleic acids, as recited by Claim 1, is that the sequence of one of the nucleic acid strands is the reverse complement of the other. That is, the sequence of one nucleic acid strand can be derived from the other by reading the sequence 3'-5' rather than 5'-3' and substituting A for T, G for C, C for G, and T for A. Thus, one of ordinary skill in the art can readily determine the metes and bounds of amended Claim 1. Accordingly, Applicants respectfully submit that Claim 1 as amended is not indefinite over the recitation of "complementary."

Claim 1 also stands rejected as indefinite over the recitation of "a probe having a binding sequence D which can bind to a sequence B located between the sequences A and C,

or to the complement thereof." The PTO asserts that if sequence D binds sequence B, it necessarily cannot bind to the sequence B'. Without acquiescing to the propriety of the rejection, Applicants have amended Claim 1 to recite that the probe comprises a sequence D which binds either to a sequence B or to the complement thereof. The methods of the invention do not depend on the strand of the amplificate to which the probe binds. Thus, the probe need not bind both sequence B and sequence B' simultaneously to be useful in the claimed methods. Rather, the methods of the invention will work equally well whether the probe binds to a sequence B, or to the complement sequence B'. Applicants respectfully submit that one of ordinary skill in the art will understand the bounds of Claim 1 as currently amended. Accordingly, Applicants respectfully submit that Claim 1 as amended is not indefinite.

Claim 3 stands rejected as indefinite over the recitation of "one of the primers has nucleotides... which do not hybridize directly with the nucleic acid to be detected." Applicants have amended Claim 3 to recite that one of the primers has nucleotides which do not hybridize with the nucleic acid to be detected. Thus, Applicants believe that one of ordinary skill in the art will recognize the scope of Claim 3 as amended. Accordingly, Applicants respectfully submit that Claim 3 as amended is not indefinite.

Claims 4 and 11-13 stand rejected over the recitation that at least one of the binding sequences, primers, or probes used in the methods of the invention "are not specific for the nucleic acid to be detected." The specification provides a definition for "not specific" in relation to a particular nucleic acid sequence at page 42, lines 13-16. Here, the specification states that a "sequence is preferably not specific for a sequence when it could hybridize with other nucleic acids under the conditions that are used to carry out the test."

Thus, a binding sequence, a primer, or a probe is not specific for a given nucleic acid to be detected when it could hybridize to one or more nucleic acids other than the particular nucleic acid to be detected under the conditions that are used to perform the method. In such embodiments of the invention, more than one nucleic acid sequence can be detected simultaneously, as described in the specification at, for example, page 49, lines 16-26. One of ordinary skill in the art can conceive of and design a primer or probe that can bind to two different nucleic acid sequences under the desired reaction conditions, according to the teaching of the specification. See, *e.g.*, the specification at page 44, line 20, to page 47, line 11. Further, the ordinarily skilled artisan is fully able to select reaction conditions to allow a primer or probe of known sequence to bind to two different nucleic acid sequences, as taught by the specification. See, *e.g.*, the specification at page 30, line 14, to page 31,

line 7. Given this definition of "not specific for the nucleic acid to be detected," Applicants believe that one of ordinary skill in the art can recognize the metes and bounds of Claims 4 and 11-13 as amended. Accordingly, Applicants respectfully submit Claims 4 and 11-13 are not indefinite.

Claim 4 also stands rejected as allegedly indefinite over the recitation of "at least one of the binding sequences is not specific for the nucleic acid to be detected" in that the binding sequences are part of the nucleic acid to be detected. Applicants earnestly thank the PTO for pointing out this inadvertent error. Applicants have amended Claim 4 to recite "at least one of the primers or probe is not specific for the nucleic acid to be detected." Thus, Applicants respectfully submit one of skill in the art can recognize the metes and bounds of Claim 4 as amended. Accordingly, Applicants respectfully submit that amended Claim 4 is not indefinite.

In view of the foregoing, Applicants respectfully submit that the rejection of Claims 1-15 as indefinite are either in error or moot in view of the amendments to the claims. Accordingly, Applicants earnestly request withdrawal of the rejection of Claims 1-15 as indefinite under 35 U.S.C. § 112, second paragraph.

V. The Rejection of Claims 1, 2, 3, 5-7, 10 and 14 under 35 U.S.C. § 102(b)

Claims 1, 2, 3, 5-7, 10 and 14 stand rejected as anticipated under 35 U.S.C. § 102(b) by Whitby and Garson, 1995, *J. Virol. Methods* 51:75-88 ("*Whitby*"). Applicants respectfully traverse the rejection of the claims on the grounds that *Whitby* does not teach each and every element of the invention as presently claimed.

A. *The Legal Standard*

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. *See* M.P.E.P. § 2131. Thus, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly "insubstantial" and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir., 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir., 1985), the Federal Circuit explained that even if the prior art teaches "substantially the same thing" as the claimed invention, the reference still cannot anticipate

the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

B. *The Claimed Invention*

The invention as presently claimed relates to a method for the detection of a nucleic acid. The method as recited by Claim 1 comprises three steps, one of which recites producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers. One of the primers binds to a binding sequence A', which is complementary to a sequence A of one strand of the nucleic acid, and the other primer binds to a binding sequence C which is located in the 3' direction from A and does not overlap A. Another step recites contacting the amplificates with a probe having a binding sequence D which binds to a sequence B located between the sequences A and C, or to the complement thereof. Yet another step recites detecting the formation of a hybrid of the amplificate and probe. The sequence located between the sequences A and C contains no nucleotides or less than three nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto, and the amplificates are shorter than 100 nucleotides.

C. *Whitby does not Teach Each and Every Element of the Claimed Invention*

Whitby teaches amplification of hepatitis C virus ("HCV") cDNA using primers to produce amplificates and detection of the amplificates using probes. As noted by the PTO, two sets of primers are used in pair-wise combination to produce amplificates of 82 base pairs, 70 base pairs, 72 base pairs, and 60 base pairs. The primers are 19 to 20 base pairs long. *See Whitby* at Table 1. The PTO also notes that the detection probes are located between base pairs 123 and 142 of the HCV cDNA. *See Whitby* at Table 1. Accordingly, the detection probes described in *Whitby* are 20 base pairs long, while the amplificates are between 60 and 82 base pairs.

As described above, Claim 1 recites that the sequence located between the sequences A and C contains no nucleotides or less than three nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto. This element of Claim 1 is not taught or suggested by *Whitby*. The shortest amplificate described by *Whitby* is 60 base pairs long, which is produced using the primers labeled PT3 and PT4. PT3 is complementary to bases 100-119 of the sense strand of the HCV cDNA. PT4 is complementary to bases 159-140 of the anti-sense strand

of the HCV cDNA. The probes that are used to detect the amplificate are each complementary to bases 123-142 of the sense strand or 142-123 of the anti-sense strand of the HCV cDNA. Thus, neither a primer nor the probe is complementary and hybridizes to bases 120-122 of the HCV cDNA.

In other words, the smallest amplificate described by *Whitby* comprises three nucleotides between the primer binding regions (*i.e.*, sequences A and C) that do not belong to the duplex formed by the probe and the amplificate (*i.e.*, sequence region E). Each of the other amplificates formed using the other primer pairs is larger than the 60 base pair amplificate discussed immediately above and have more than three nucleotides that are not part of sequences A, C, or E. Accordingly, *Whitby* does not teach or suggest methods of detecting a nucleic acid wherein the sequence located between the binding sequences A and C contains no nucleotides or less than three nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto, as recited by Claim 1.

Applicants note parenthetically that there is no motivation or suggestion in *Whitby* to modify the methods disclosed therein to detect a nucleic acid using methods wherein there are no or less than three nucleotides that are not part of sequences A, C, or E. *Whitby* does not suggest that the methods for detecting a nucleic acid disclosed therein could be improved by further minimizing the size of the amplificate by selecting the primers and probes such that there are less than three nucleotides that are not part of sequences A, C, or E. Indeed, *Whitby* does not provide any direction at all for further optimization of the described methods. In contrast, Applicants have discovered a significant advantage to use of methods wherein there are no nucleotides or less than three nucleotides that are not part of sequences A, C, or E at, for example, page 28, lines 18-29, of the specification. Here, Applicants explain that such methods ameliorate the disadvantages of forming longer amplification products while still maintaining specificity for the nucleic acid to be detected. *Whitby* discusses neither these disadvantages nor methods of overcoming these disadvantages.

In particular, *Whitby* does not even recognize the disadvantages presented by forming longer amplification products according to the methods described therein. As *Whitby* does not recognize these disadvantages, it cannot teach or suggest that they could be overcome by minimizing the size of the amplificate by selecting the primers and probe such there are no nucleotides or less than three nucleotides that are not part of sequences A, C, or E. Thus, *Whitby* does not provide motivation or suggestion to modify its teaching to use methods wherein there are no nucleotides or less than three nucleotides that are not part of sequences

A, C, or E as recited by, for example, Claim 1 of the present application. Accordingly, the claims of the present application are not obvious over *Whitby*.

Because *Whitby* does not teach or suggest each and every element of the invention as presently claimed, *Whitby* does not and cannot anticipate Claims 1, 2, 3, 5-7, 10 and 14. Therefore, Applicants respectfully request that the rejection of Claims 1, 2, 3, 5-7, 10 and 14 as anticipated under 35 U.S.C. § 102(b) be withdrawn.

VI. The Rejection of Claims 8, 9, and 15 under 35 U.S.C. § 103(a)

Claims 8, 9, and 15 stand rejected as obvious under 35 U.S.C. § 103(a) over *Whitby* in view of U.S. Patent No. 5,538,848 ("the '848 patent"), U.S. Patent No. 6,245,514, ("the '514 patent"), or International Patent Publication No. WO 96/29431 ("the '431 publication"), respectively. Applicants respectfully traverse the rejection on the grounds that the cited references do not teach each and every element of the invention as presently claimed.

A. *The Legal Standard*

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be prima facie obvious over the prior art. *See In re Bell*, 26U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention prima facie obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the

motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a prima facie case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. *The Cited References do not Teach or Suggest Each and Every Element of the Claimed Invention*

The PTO supports the rejection of Claims 8, 9, and 15, in part, on the same portions of *Whitby* as were cited in the rejection of Claims 1, 2, 3, 5-7, 10 and 14 as anticipated. In particular, the PTO relies upon *Whitby* to teach or suggest amplification of HCV cDNA using primers to produce amplificates, and detection of the amplificates using probes.

As shown above, *Whitby* does not teach or suggest methods of detecting a nucleic acid wherein the sequence located between the binding sequences A and C contains no nucleotides or less than three nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplificate bound thereto, as recited by Claim 1.

Furthermore, neither the '848 patent, the '514 patent, nor the '431 publication teach or suggest the detection of a nucleic acid using methods wherein there are no nucleotides or less than three nucleotides that are not part of sequences A, C, or E. The '848 patent teaches methods of detecting amplificates using self-quenching fluorescent probes and is silent as to the number of nucleotides that are not part of sequences A, C, or E. Similarly, the '514 patent teaches methods of using specific fluorescent donor-acceptor pairs and also is silent as to the number of nucleotides that are not part of sequences A, C, or E. Finally, the '431 publication teaches methods of detecting nucleic acids using mass spectroscopy and is likewise silent as to the number of nucleotides that are not part of sequences A, C, or E. Thus, none of the '848 patent, the '514 patent, or the '431 publication teaches or suggests the detection of a nucleic acid using methods wherein the sequence between the primer binding regions contains no nucleotides or less than three nucleotides that are not hybridized to the probe.

As Claims 8, 9, and 15 each depend from Claim 1, each of the rejected claims require that the sequence between the primer binding regions contain no nucleotides or less than

three nucleotides that are not hybridized to the probe. Therefore, the cited references, even if they could be validly combined, do not teach each and every element of Claims 8, 9, and 15. Accordingly, Applicants respectfully submit that the rejection of these claims as obvious over *Whitby* in view of either the '848 patent, the '514 patent, or the '431 publication is erroneous and respectfully request its withdrawal.

VII. RELATED APPLICATIONS

For the PTO's convenience, Applicants identify applications related to the currently pending matter.

Including the present application, Applicants have four pending applications relating to specific and sensitive methods for detecting nucleic acids, as described in Table 1, below. U.S. Application No. 10/322,138 is a divisional application of the present application.

U.S. Application No.	Filing Date	Attorney Docket No.
09/530,746	May 4, 2000	1803-277-999
09/530,747	May 4, 2000	1803-302-999
09/530,929	May 4, 2000	1803-303-999
10/322,138	December 17, 2002	1803-356-999

CONCLUSION

Applicants respectfully submit that Claims 1-15 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1-15 to issuance is therefore kindly solicited. If the PTO believes that a telephone call would resolve any remaining issues, the PTO is invited to telephone the undersigned attorney at (650) 849-7607.

No fees is believed due in connection with this amendment. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150 (1803-277-999).

Respectfully submitted,

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